Please amend the paragraph on page 4, line 27 to page 5, line 2, to read as follows:

C1 --There are three mechanisms (not mutually exclusive) of staining that have been suggested by the research to date: 1) mucopolysaccharide staining with metachromasia (a concomitant shift in the absorption spectra of the phenothiazine compound); 2) enhanced nuclei and nucleoli staining (RNA- and DNA-rich) associated with enhanced proliferation of these organelles in pre-cancerous and cancerous cells; and 3) enhanced staining of the mitochondria of metaplastic (dysplastic, pre-cancerous, and cancerous) cells.--

Please amend the paragraph on page 5, lines 19-24, to read as follows:

C2 --Despite the apparent sensitivity of methylene blue for metaplastic cells and tissue, toluidine blue O, also a thiazine dye, has found more widespread application. Sugerman, et al. (*Arch. Surg.* 1970 Mar.;100(3):240-3) uses toluidine blue in the diagnostic stain of neoplastic lesions. Chesser, et al. (*J. Dermatol. Surg. Oncol.* 1992 Mar.;18(3):175-6) recommend using toluidine blue O, *ex vivo*, as a staining technique for the treatment of adenoid cystic carcinoma by Mohs micrographic surgery.--

Please amend the paragraph on page 8, lines 14-20, to read as follows:

C3 --The histochemical pathology of dysplastic, pre-cancerous, and cancerous lesions that would be expected to be stained with any of the thiazine dyes will vary as to the degree of *metachromasia* within the cell tissue layer. This depends on the variation in mucin production, aberration of nuclei, nucleoli, and mitochondrial organelle distribution, as well as changes in cell membrane permeability, charge structure and membrane transport properties, etc., with the various cell types associated with each diagnosis and the stage of metaplasia or cell transformation.--

Please amend the paragraph on page10, lines 17-22, to read as follows:

--U.S. Patent 5,784,162 teaches multi-variant spectral bio-imaging analysis for diagnostics and therapy utilizing optical means including two-dimensional photodetector arrays. Requiring sample preparation and visualization, the method incorporates, in part, fluorescent dyes to enhance imaging but makes no reference to the utility of spectrum analysis of metachromasia or differential biological staining of tissue or cells as a means of correlating metaplastic stage.--

Please amend the paragraph on page 10, lines 24-29, to read as follows:

C4

--U.S. Patent 4,973,848 uses a pair of laser beams in the course of photodynamic therapy where one beam is used to analyze the surface to be treated as a means of controlling the properties of the "treatment" beam but makes no reference to the utility of spectrum analysis of metachromasia or differential biological staining of tissue or cells as a means of correlating metaplastic stage. Further, the analysis is limited to the wavelength of the analysis laser beam rather than a broad spectrum of light energy.--

Please amend the paragraph on page 11, lines 1-6, to read as follows:

--Complex biological stain compositions for histological examinations are taught in U.S. Patent No. 4,595,582. These dyestuff compositions, of which some components are of the thiazine family, are an improvement to conventional histochemical methods, enhancing visualization of cytological structure within fixed tissue. It does not teach or make reference to the utility of spectrum analysis of metachromasia or differential biological staining of tissue or cells as a means of correlating metaplastic stage.--

Please amend the paragraph on page 20, lines 1-17, to read as follows:

--The use of biological stain in direct staining *in vivo* has been shown to have a high degree of sensitivity to a variety of metaplastic, pre-cancerous and cancerous cells and tissues. For example, the thiazine dyes toluidine blue O and methylene blue have found frequent use in the *in vivo* diagnosis of oral epithelial carcinomas, dermal epithelial carcinomas, esophageal cancer, cervical and vaginal cancers, and even in the detection of bladder cancers. However, the specificity of the staining process in differentiating between the stage and type of metaplasia has been variable and has not allowed for a definitive diagnosis of the disease state. Generally, vital or *in vivo* staining has not been able to distinguish between normal cellular repair process and metaplasia. Practitioners have used the sensitivity of the stains to locate diseased tissue and then subsequently relied on biopsy and classical histochemical techniques for a final diagnosis. Histochemical methods further rely on staining the morphological as well as the biochemical features retained after the fixation and sectioning of the tissue sample. The staining features of intensity and color are then examined and a subjective, if skilled, determination as to the underlying cell type is rendered as the diagnosis.--

Please amend the paragraph on page 21, line 29 to page 22, line 20, to read as follows:

--The analysis of the reflectance spectrum of the stained tissue area by software means is significant to the present invention. It may be conducted in a variety of ways to fulfill the intent of this method. For example, the software analysis of the spectra may compare the metachromatic shift of the stain toluidine blue O between two or more specific wavelengths by correlation. The results are then compared to a body of data previously collected and correlated to underlying conventional histochemical data defining the cellular stage of metaplasia. It can readily be seen that a combination of two stains, for example, methylene blue and pyronin Y, applied either from one composition or applied as two separate preparations and analyzed by comparative spectrometric means and suitable software analysis, may afford a desirable degree of

enhanced specificity in certain applications. The two stains would compete for certain histochemical features that would distinguish cells undergoing normal repair processes and those cells that are metaplastic or neoplastic. Further additional diagnostic utility may be afforded by means of monitoring the photooxidation of the specific stain or stain composition by spectrometric means and analyzing the resulting change in the spectra, correlating the result to underlying clinical analysis of the procedure verified by conventional means. The photooxidation may be by means of a broad-spectrum high intensity light source (either through the fiber optic bundle or external to the fiber optics), a filtered high intensity light source, or by means of a specific wavelength laser. In this manner of analysis, the change in the characteristic spectrum of the measured tissue stain combination (in other words, the photobleaching process; i.e., *"photochromasia")* may be followed as a function of time, intensity, or a combination thereof.

C16

Please amend the paragraph on page 22, line 27 to page 23, line 10, to read as follows:

--It can be further seen that this *in situ* diagnostic method may be extended to a highly controlled phototherapeutic method for the destruction and removal of diseased tissue and cells. It has been seen that many biological stains, for example, particularly the thiazine family, such as methylene blue and toluidine blue O, have found application as photosensitizers for photodynamic therapy. Because of the specificity of these biological stains for metaplastic cells, including cancerous cells, the photooxidation results in a cytotoxic effect. It may be highly advantageous to the practitioner to be able to assess the cytological state of an area of tissue in applying irradiation for phototherapeutic means, for example, allowing discrimination between highly metaplastic tissue as compared to inflamed but otherwise normal tissue area and cells undergoing the normal repair processes. This would minimize, for example, the amount of tissue destruction by means of a high power laser. Further, the course of the phototherapy up to a defined end point can be accurately and carefully assessed using

C17